PATENT COOPERATION TRFATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 September 2000 (25.09.00)	
International application No. PCT/NL00/00013	**Applicant's or agent's file reference** P48358PC00
International filing date (day/month/year) 10 January 2000 (10.01.00)	**Priority date** (day/month/year) 11 January 1999 (11.01.99)
Applicant NOTEBORN, Mathieu, Hubertus, Maria et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 August 2000 (10.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL BUREAU OTTEVANGEN

To:
OTTEVANGERS, S., U.
Vereenigde
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

14 AUG 2000

AMERSFOORT

NRF 11-9-2000 Gum

Prel. ex. 11-8-2000 Gum

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Kopie in/naar

TERMIJN

07 AUG. 2000

Date of mailing (day/month/year)	Applicant's or agent's file reference
20 July 2000 (20.07.00)	MAP P48358PC00

IMPORTANT NOTICE

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/NL00/00013	10 January 2000 (10.01.00)	11 January 1999 (11.01.99)

Applicant
LEADD B.V. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   20 July 2000 (20.07.00) under No. WO 00/41497

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P48358PC00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 00/ 00013	10/01/2000	11/01/1999
Applicant		
LEADD B.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 00/00013

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/16 A61K48/00 G01N33/50 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, BIOSIS, CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 37901 A (BOEHRINGER INGELHEIM PHARMA ;MARLIN STEVEN D (US); TATAKE REVATI J) 3 September 1998 (1998-09-03)	1-6, 9-12,14
Y	page 7, line 24 -page 9, line 10 page 11, line 5 -page 17, line 7 ---	7,8
X	EP 0 866 131 A (SANKYO CO) 23 September 1998 (1998-09-23)	1-6, 9-12,14
Y	page 2, line 3 -page 4, line 1 ---	7,8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2000	17/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sitch, W

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE 'Online! FILE SERVER STN KARLSRUHE; ABSTRACT NO. 1998352185, "Apoptin specifically causes apoptosis in tumor cells and after UV-treatment in untransformed cells from cancer-prone individuals: a review." XP002107637	2,5, 11-15
Y	abstract	7,8
A	& MUTATION RESEARCH, (1998 MAY 25) 400 (1-2) 447-55. REF: 52 JOURNAL CODE: NNA. ISSN: 0027-5107.,	16

X	WO 98 46760 A (PIETERSEN ALEXANDRA MARIA ;LEADD B V (NL); NOTEBORN MATHEUS HUBERT) 22 October 1998 (1998-10-22) cited in the application	2,5, 11-14
Y	page 4, paragraph 2 -page 5, paragraph 1	7,8

X	WO 96 41191 A (AESCULAAP BV) 19 December 1996 (1996-12-19)	2,5, 11-14
Y	page 5, line 9 -page 9, line 21	7,8

Y	DE 197 04 979 A (MAX DELBRUECK CT FUER MOLEKULA) 14 August 1997 (1997-08-14) page 2, line 3 - line 5 page 2, line 38 - line 44 example 1	7,8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 00/00013

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9837901	A	03-09-1998	AU	6672498 A	18-09-1998
			BR	9807622 A	15-02-2000
			CN	1249688 T	05-04-2000
			EP	0989853 A	05-04-2000
			PL	335409 A	25-04-2000
EP 0866131	A	23-09-1998	AU	5937598 A	15-10-1998
			BR	9800937 A	11-01-2000
			CA	2232828 A	21-09-1998
			CZ	9800858 A	14-10-1998
			HU	9800613 A	01-02-1999
			JP	10324699 A	08-12-1998
			NO	981272 A	22-09-1998
			NZ	330004 A	28-10-1998
			PL	325457 A	28-09-1998
			ZA	9802371 A	28-09-1998
WO 9846760	A	22-10-1998	EP	0872552 A	21-10-1998
			EP	0878546 A	18-11-1998
			AU	6856398 A	11-11-1998
			EP	0975764 A	02-02-2000
			NO	994967 A	15-12-1999
WO 9641191	A	19-12-1996	AU	718422 B	13-04-2000
			AU	5913696 A	30-12-1996
			CA	2221495 A	19-12-1996
			EP	0830604 A	25-03-1998
			JP	11506340 T	08-06-1999
			US	5958424 A	28-09-1999
DE 19704979	A	14-08-1997	WO	9729201 A	14-08-1997

PATENT COOPERATION TREATY + 2000

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Gedeeltelijk per PCT → LP

To:

PRINS, A.W.
VEREENIGDE
Nieuwe Parklaan 97
NL-2587 BN The Hague
PAYS-BAS

NRT₂ 11-7-2000

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

TERMIJN	
30 MRT 2001	
Beantwoord / Voorl. / def.	Bericht gezonden aan / dd. 4/5/01
MAP	Applicant's or agent's file reference: P48358PC00

Date of mailing *(day/month/year)*: 27.03.2001

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00013	10/01/2000	11/01/1999

Applicant: LEADD B.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P48358PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00013	10/01/2000	11/01/1999
International Patent Classification (IPC) or national classification and IPC A61K38/16		
Applicant LEADD B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/08/2000	27.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00013

I. Basis f th r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-31	as originally filed	

Claims, No.:

7-16	as originally filed	
1-6	with telefax of	08/01/2001

Drawings, sheets:

1/1	as originally filed	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-14.

because:

- ☒ the said international application, or the said claims Nos. 1-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
  see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  see separate sheet

- ☒ the claims, or said claims Nos. 1-14 are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with r gard to novelty, inv ntive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	15-16
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	15-16
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	15-16
	No:	Claims	-

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the opinion

Added subject matter (Art. 34 (2)(b) PCT) - see items III 1- and 1.1- below.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Claims 1-5 have been amended to stress the fact that the apoptosis inducing agent according to the present application exhibits its effect in the aberrant cells involved with or related to autoimmune diseases.

However, (see p 5 lines 32-37) " a very important advantage of apoptin over other apoptosis inducing agents is that it does not display its activity to any significant extent in normal cells, whereas the present application shows that it does exhibit its effect in the aberrant cells involved with or related to inflammatory disorders and/or (auto)immune diseases". In addition, as shown e. g. on p 9 lines 33-38, p 18 lines 1-6 and p 24 lines 27-31, the present application only provides technical support for the use of apoptin, since only apoptin is shown in the present application to provide the aimed effect, i. e. non induction of apoptosis in normal healthy cells and induction of cell death in aberrant cells involved with or related to inflammatory disorders and/or (auto)immune diseases.

Hence, the subject matter claimed in the present application should be restricted to (see e. g. p 8 lines 7-10) " the apoptosis inducing protein apoptin or other proteins with apoptin-like activity".

1.1- The amendments filed with the letter dated 08.01.2001 (claims 1-5): "an apoptosis inducing agent which exhibits its effect in aberrant cells involved with or related to (auto)immune diseases", are a generalization of the apoptosis inducing agent apoptin (only apoptin is shown in the present application to provide the aimed effect, i. e. non induction of apoptosis in normal healthy cells and induction of cell death in aberrant cells involved with or related to inflammatory disorders and/or (auto)immune diseases) and therefore introduce subject-matter which extends beyond the content

of the application as filed, contrary to Article 34(2)(b) PCT.

Therefore, no opinion will be given with regards to the novelty, inventive step and industrial applicability of claims 1-5 and their dependent claims 6-14.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2- Reference is made to the following documents:

D1: WO 98 37901 A (BOEHRINGER INGELHEIM PHARMA ;MARLIN STEVEN D (US); TATAKE REVATI J) 3 September 1998 (1998-09-03)

D2: EP-A-0 866 131 (SANKYO CO) 23 September 1998 (1998-09-23)

D3: DATABASE MEDLINE [Online] FILE SERVER STN KARLSRUHE; ABSTRACT NO. 1998352185, 'Apoptin specifically causes apoptosis in tumor cells and after UV-treatment in untransformed cells from cancer-prone individuals: a review.' XP002107637 & MUTATION RESEARCH, (1998 MAY 25) 400 (1-2) 447-55. REF: 52 JOURNAL CODE: NNA. ISSN: 0027-5107.,

D4: WO 98 46760 A (PIETERSEN ALEXANDRA MARIA ;LEADD B V (NL); NOTEBORN MATHEUS HUBERT) 22 October 1998 (1998-10-22) cited in the application

D5: WO 96 41191 A (AESCULAAP BV) 19 December 1996 (1996-12-19)

D6: DE 197 04 979 A (MAX DELBRUECK CT FUER MOLEKULA) 14 August 1997 (1997-08-14)

NOVELTY - Art. 33 (1) and (2) PCT

3- Claims 15 and 16 appear to be novel in the light of the available prior art and for the reasons stated below:

3.1- The novel feature appears to be the use of "apoptin like activity" (see objection item VIII 7-) for determining (1) the presence of cells likely to result in an (auto)immune

disease and/or (2) the presence of autoimmune diseases.

D3, D4 and/or D5, which disclose the use of apoptin, do not explicitly mention that apoptin can also induce apoptosis in cells of inflammatory disorders and/or autoimmune diseases. Therefore, D3, D4 and/or D5 are not novelty destroying for claims 15-16.

Remark: The term "immune disease" has been interpreted, for the purpose of this opinion, as an aberrant behaviour of the immune system, leading for example to hyperactivity of the immune system.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

4- The present application is based on the finding that apoptin does not display its activity to any significant extent in normal cells, whereas it does exhibit its effect in the aberrant cells involved with or related to inflammatory disorders and/or (auto)immune diseases

This discovery is neither explicitly disclosed and nor suggested by the available prior art documents, alone or combined.

4.1- The problem posed in the present application is therefore to provide means for the treatment of inflammatory / (auto)immune disorders.

The solution proposed is the use of the apoptosis inducing protein apoptin or other proteins with apoptin-like activity.

D1 and D2 disclose the use of apoptosis inducing agents for the treatment of inflammatory and/or (auto)immune disorders and hence represent the closest prior art.

However, neither D1, nor D2 alone or combined teach or suggest the use of apoptin.

4.2- D3 mentions that apoptin induces apoptosis in human transformed/tumorigenic cells but not in normal diploid cells.

However, the term "immune disease" has been interpreted, for the purpose of this opinion, as an aberrant behaviour of the immune system, leading for example to hyperactivity of the immune system.

Hence, the subject matter of claims 15-16 is not obvious from the available prior art and claims 15-16 can be considered as being inventive.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

5- Claims 15-16 appear to be industrially applicable.

Re Item VIII

Certain observations on the international application

6- As far as claims 1-5 and dependent clams 6-14 are concerned, the following is to be noted:

If claims 1-5 (and dependent claims 6-14) were restricted (see item III 1-)to the use of " the apoptosis inducing protein apoptin or other proteins with apoptin-like activity", said claims could be considered as being novel over D1 and over D2, since neither D1 nor D2 explicitly mention the use of " the apoptosis inducing protein apoptin or other proteins with apoptin-like activity".

7- The expression: "providing suspect cells with apoptin-like activity" (claims 15-16) is not clear (Art. 5 PCT) and should be clarified in terms of the agent which is provided (and not of the activity which is provided).

AMENDED CLAIMS

1. Use of an apoptosis inducing agent, which exhibit its effect in aberrant cells involved with or related to (auto) immune diseases, in the preparation of a medicament for the treatment of inflammatory disorders.

2. Use of an apoptosis inducing agent, which exhibit its effect in aberrant cells involved with or related to (auto) immune diseases, in the preparation of a medicament for the treatment of immune diseases.

3. Use of an apoptosis inducing agent according to claim 2 wherein said treatment of immune diseases is treatment of autoimmune diseases.

4. Use of a gene delivery vehicle comprising a gene capable of expressing an apoptosis inducing agent, which exhibit its effect in aberrant cells involved with or related to (auto) immune diseases, in the preparation of a medicament for the treatment of inflammatory disorders.

5. Use of a gene delivery vehicle comprising a gene capable of expressing an apoptosis inducing agent, which exhibit its effect in aberrant cells involved with or related to (auto) immune diseases, in the preparation of a medicament for the treatment of immune diseases.

6. Use of a gene delivery vehicle according to claim 5 wherein said treatment of immune diseases is treatment of autoimmune diseases.

7. Use according to anyone of claims 4-6, wherein said gene delivery vehicle further comprises a suicide gene.

8. Use according to claim 7, wherein said suicide gene is inducible.

9. Use according to anyone of claims 4-8, wherein said gene delivery vehicle has a tropism for hematopoietic cells.

10. Use according to claim 4-8, wherein said gene delivery vehicle has a tropism for fibroblast-like synoviocytes.